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Pathophysiology of hidradenitis suppurativa: a systematic review of the literature

Fisiopatologia da hidradenite supurativa: uma revisão sistemática da literatura

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Abstract

Hidradenitis suppurative (HS) is a multifactorial, recurrent, chronic inflammatory disease with a significant impact on patient's quality of life. The etiopathogenesis of this complex condition is not fully understood. In this systematic review, we aimed to address and clarify the role of genetics, immunity, endocrinology, and skin microbiome together with risk factors in HS etiopathogenesis. A systematic review, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, was performed using PubMed® and Web of Science™ databases on December 3rd, 2021, using patient/population, intervention, comparison and outcomes (PICO) criteria, limited to the last 10 years and English. Reports were analyzed by two independent reviewers. A total of 123 reports were included and divided into five sections: genetics, immunity, endocrinology, microbiome, and risk factors. Regarding genetics, up to 30-40% of patients have a positive family history of HS but only a small subset of these harbor genetic variants in components of the gamma-secretase complex. In fact, in more than 90% of HS patients, the genetic features contributing to disease development remain largely unknown. The immune response is also crucial for HS; it is characterized by antimicrobial peptide and proinflammatory cytokine dysregulation, namely interleukin (IL)—IL-23, IL-12, and Th17 immune response. This immune response in local and, consequently, systemic inflammation is amplified in patients with metabolic syndrome. The relationship between metabolic syndrome and HS is clear, and patients with metabolic syndrome have a higher risk of developing HS. The most recent evidence also associates skin microbiota dysbiosis with HS pathogenesis, contributing to local and systemic inflammation. Besides these intrinsic factors, the role of lifestyle in the development of HS is well accepted. Tobacco smoking and obesity are the main risk factors identified as contributing to HS pathogenesis. Chronic inflammation characterizes HS, a debilitating condition with a complex and multifactorial etiopathogenesis. The current model integrates genetics, immunity, endocrinology, and skin microbiome. Notwithstanding, efforts should be made to improve our comprehension of HS etiopathogenesis, hopefully leading to the development of more effective treatments.

Keywords: Gamma-secretase complex. Etiopathogenesis. Risk factors. Hidradenitis suppurativa. Immunity. Microbiome.

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Resumo

A hidradenite supurativa (HS) é uma doença inflamatória, multifatorial, recorrente e crónica com um impacto significativo na qualidade de vida dos doentes. A etiologia desta condição complexa não é totalmente compreendida. Nesta revisão sistemática, pretende-se abordar e clarificar o papel da genética, imunidade, endocrinologia, microbioma cutâneo e fatores de risco que contribuem para o desenvolvimento da HS. A revisão sistemática, seguindo as orientações PRISMA, foi realizada através de uma pesquisa bibliográfica nas bases de dados PubMed® e da Web of Science™ a 3 de dezembro de 2021, utilizando critérios do PICO, e limitada aos últimos 10 anos e inglês. Os estudos a serem incluídos foram analisados por dois revisores independentes. Um total de 123 estudos foram selecionados e divididos em cinco secções: genética, imunidade, endocrinologia, microbioma e fatores de risco. Em relação à genética, cerca de 30-40% dos doentes têm uma história familiar positiva de HS, mas as variantes genéticas das componentes do complexo da gama secretase só estão identificadas num número reduzido de doentes. De facto, em mais de 90% dos doentes com HS, a componente genética que contribui para o desenvolvimento da doença permanece desconhecida. A resposta imunitária é também crucial para a HS: caracteriza-se pela desregulação dos péptidos anti-microbianos assim como das citocinas pró-inflamatórias, nomeadamente IL-23, IL-12 e resposta Th17. Esta resposta que ocorre na inflamação local e consequentemente sistémica é exacerbada em doentes com síndrome metabólica. A relação entre a síndrome metabólica e a HS é clara, e os doentes com síndrome metabólica tem um risco elevado para o desenvolvimento de HS. As evidências mais recentes correlacionam também a disbiose do microbioma cutâneo com a patogénese da HS, contribuindo para a inflamação local e sistémica. Além destes fatores intrínsecos, o papel do estilo de vida no desenvolvimento da HS está bem estabelecido. O tabagismo e a obesidade são os principais fatores de risco identificados que contribuem para a patogénese da HS. A inflamação crónica caracteriza a HS, uma condição debilitante com uma etiologia complexa e multifatorial. O presente modelo integra a genética, a imunidade, a endocrinologia e o microbioma cutâneo, e poderá contribuir para o desenvolvimento de tratamentos mais eficazes.

Palavras-chave: Complexo gamma-secretase. Etiologia. Fatores de risco. Hidradenite supurativa. Imunidade. Microbioma.

Introduction

Hidradenitis suppurativa is a multifactorial, recurrent, chronic inflammatory condition with a significant impact on a patient's quality of life. The epidemiology of HS is not well established, but some studies indicate a prevalence of 1% in the European population[1]. There is no available epidemiological HS data regarding the Portuguese population. A study by Santos et al. evaluated Portuguese hospitalized patients with HS and concluded that the highest incidence rate occurred between 20 and 29 years old in females and 40 and 49 years old in males[2].

The onset of the disease usually occurs after puberty. HS frequently affects apocrine gland-bearing skin, mainly in the axilla, groin, breast area, gluteal and perineal regions. The initial pathophysiology of HS is probably related to alterations of the infundibular epithelium leading to follicular "plugging" and subsequent stasis of follicular content, propagation of resident bacteria, and dilation of the hair follicle unit. This cascade occurs in a background of immune dysfunction, both innate and adaptive[3-6].

HS is frequently neglected, with a subsequent delay in diagnosis, which contributes to a dramatic decrease in patients' quality of life. The patient's delayed referral may have an impact on the optimal time frame for the beginning of treatment in a disease in which the sooner the treatment is started, the better the outcome will be.

The number of publications concerning HS has increased significantly in recent years as a direct consequence of increased awareness of the disease among clinicians of different specialties. Moreover, the knowledge regarding the contribution of genetics, microbiome, immunity, endocrinology, and environmental risk factors for the pathophysiology of the disease has advanced enormously (Fig. 1). Notwithstanding, it remains a complex condition with multifactorial etiopathogenesis that is yet to be fully understood, requiring a multidisciplinary approach[5].

The aim of this systematic review of the literature is to summarize the most recent advances in the knowledge of the pathophysiology of HS, thus contributing to a better understanding of the disease and, consequently, to improved management of patients with HS.

Methods

This review followed the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA)[7].

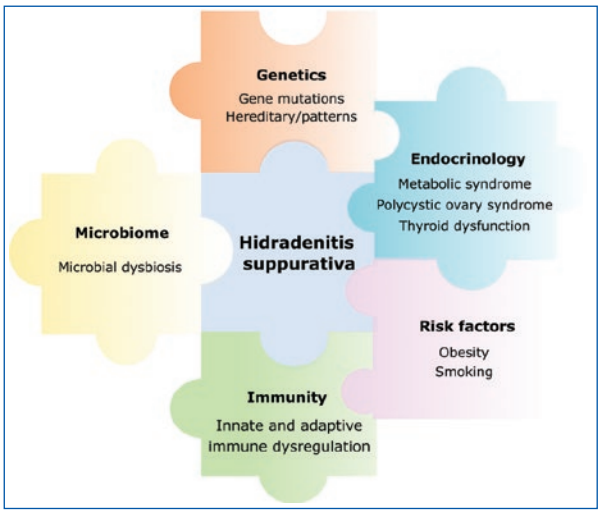

Figure 1. Overview of HS pathophysiology.

The PubMed® and the Web of Science™ databases were searched on December 3rd, 2021, using the strings "hidradenitis suppurativa AND (hormone* OR female hormone* OR androgen converting enzyme* OR obesity OR endocrinology OR contraceptive* OR androgen* OR estrogen* OR puberty OR hirsutism OR polycystic ovary syndrome OR finasteride)," "hidradenitis suppurativa AND (genetic* OR genetic signature OR gamma secretase (GSC) complex mutation* OR PSENEN OR PSEN1 OR NCSTN OR NOTCH)," "hidradenitis suppurativa AND (innate Immunity OR adaptative immunity OR cytokine* OR tumor necrosis factor alpha (TNF-α) OR IL-13 OR IL-23 OR IL-1 OR IL-17 OR IL-36 OR IL-6 OR autoimmunity OR follicular occlusion OR folicular rupture OR defensin* OR complement OR autoinflammation OR AMP*)," "hidradenitis suppurativa AND (skin microbiome OR microbiome OR pathogen* OR bacterial colonization OR biofilm* OR antibiotic*), hidradenitis suppurativa AND (risk factor* OR smoking OR nicotine OR electronic cigar* OR obesity OR intestinal inflammatory disease* OR rheumatologic* disease* OR professional risk OR labor risk OR occlusion OR friction OR hyperhidrosis OR cannabinoid*)," limited to papers written in English and published in the last 10 years. The papers obtained from these searches were joined and the duplicates were removed. Afterward, these papers were divided into five main fields that included endocrinology, genetics, immunity, microbiome, and risk factors. All the abstracts from each field were reviewed by two different authors. Reviews, case reports, and case series were not considered.

Results

A detailed flow chart with the results of the literature search is shown in Figure 2. We exported 4342 references from PubMed and Web of Science, and after the removal of duplicates and records without available abstracts, a total of 1277 references were retained. From this total of 1277 studies, divided into five main fields, 1168 were excluded by applying the selection criteria (959 by title and abstract and 209 that include treatment approach, which is out of the scope of the review). Fourteen additional studies were identified through reference tracking, citation, and grey literature. Finally, 123 studies were included in this review.

Genetics

Among patients with HS, up to 40% have a familiar history of the disease showing autosomal dominant inheritance with incomplete penetrance[8]. Causative monogenic mutations are rare and only explain 5% of HS cases[9]. Moreover, the family history of HS impacts the onset of the disease: early onset is associated with a family history of HS and with the development of inflammatory lesions at a higher number of body sites[10,11]. However, the full contribution of genetics has not been fully elucidated. A cross-sectional Dutch Twin Cohort showed that 1.2% (58 of 4686) of the twin pairs included in the study had HS with narrow-sense heritability of 77%[12]. The remaining variance is due to environmental factors supporting the multifactorial characteristic of the disease[12]. This polygenic and multifactorial pattern was recently corroborated in a nationwide registry study of Danish twins that estimated the relative importance of genetic and environmental factors underlying susceptibility to HS. This study showed that among the 170 twins with a HS diagnosis, gene-gene interactions are the likely cause of HS rather than unique mutations[9].

Some specific genes have been associated with the development of HS. GSC complex is a multi-subunit protease complex consisting of presenilin-1 (PSEN1)/presenilin-2 (PSEN2), presenilin enhancer gamma-secretase subunit (PSENEN), nicastrin (NCSTN), and anterior pharynx defective 1a (APH1A)/anterior pharynx defective 1b (APH1B). This complex is essential for the maturation of hair follicle cells and for normal immune system function[13]. Studies have demonstrated that loss-of-function mutations in the components of this complex lead to decreased protease cleaving activity, probably compromising canonical Notch signaling[14].

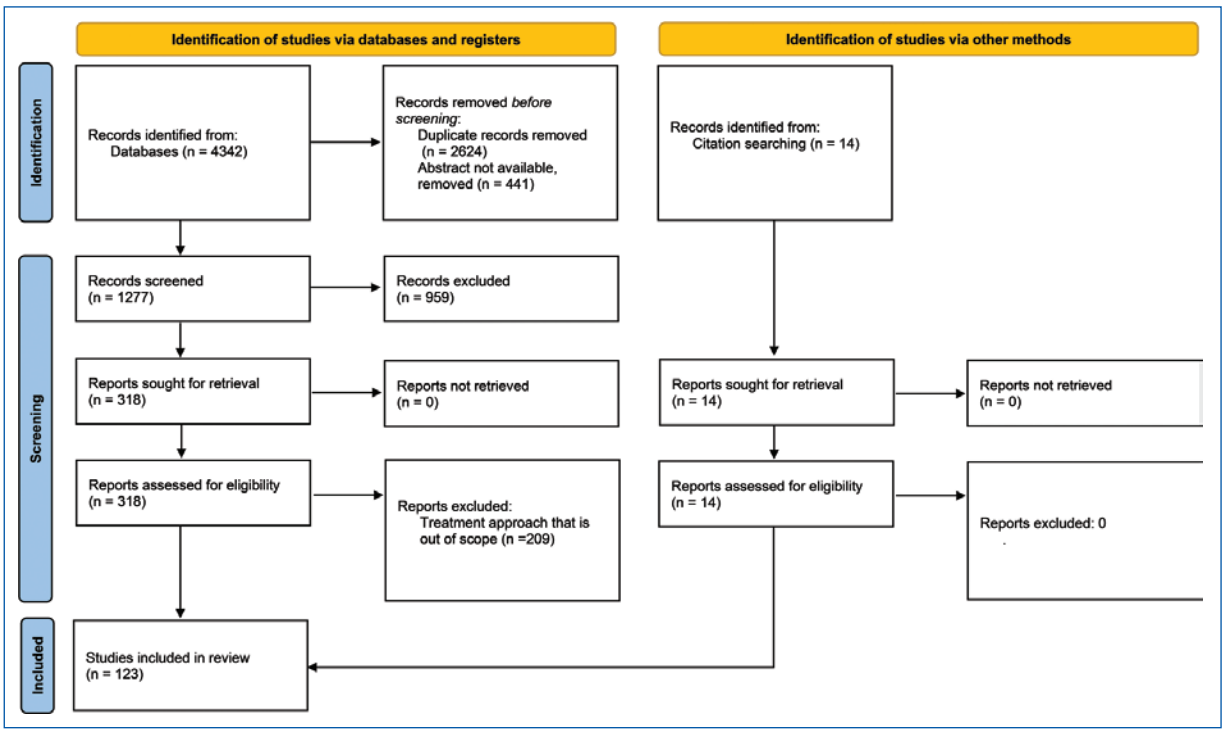

Figure 2. PRIMA flow for systematic review of the literature adapted from Page MJ (2021)[7].

The mutations in NCSTN are responsible for cases of familial HS by regulation of in vitro keratinocytes' inflammatory responsiveness through the Notch and PI3K/AKT signaling[8,15]. PSENEN mutations alone seemed to be insufficient to cause HS[3]. An in silico study demonstrated that mutations in GSC associated with HS have a structural impact and potentially also functional impact on the GSC, namely substrates receptor tyrosine-protein kinase (ErbB4), sodium channel subunit beta-1 (SCNB1), and tyrosine kinase with immunoglobulin-like and EGF-like domains 1 (Tie1), that could contribute to a genetic signature of HS[16]. Besides the known loss-of-function mutation in the GS complex, a splice site mutation, c.582-1delG in NCSTN, was identified in Japanese familial HS[17].

Beyond these in vitro and in silico studies, there are also clinical studies aiming to address the genetic/genomic alterations in patients/families with HS. Apart from GSC genes, other genetic factors are also important in the pathophysiology of HS. Genes directly related to the IL-12/IL-23-Th17 pathway[18], β-defensin genes (namely DEFB4 and DEFB103)[19], sphingolipid metabolism pathway[20], DNA hydroxymethylation regulators[21], and human leukocyte antigen system (HLA)[22], have already been associated with HS (Table 1).

Immunity

HS should be classified as an immune-mediated disease.[5] The initial events in the development of HS can trigger an exaggerated response of the cutaneous immune system, resulting in the transformation of mild acute events into chronic inflammation of affected skin areas with the formation of recurrent nodules and dermal tunnels (Figure 3A)[5].

Disease progression can lead to systemic inflammation, amplifying the local inflammatory cascade and probably facilitating extracutaneous comorbidities.[5] Despite the consensus that immune dysregulation plays a major role in the development of chronic inflammatory lesions in HS, critical details such as specific cytokines and pathways involved, immune signature, and relative contributions from both innate and adaptative immune systems remain to be properly clarified. Figure 3B schematizes the findings in lesional and perilesional HS skin and relevant serum biomarkers reflecting the impact of immunity in the physiopathology of HS.

Innate immunity is crucial for developing HS[28,29]. This was demonstrated by the up-regulation of messenger RNA (mRNA) levels of antimicrobial peptides (AMP)[30] and proteins such as human-β-defensin 1 (hBD-1), hBD-2, and hBD-3, cathelicidin (LL-37), ribonuclease 7 (RNase 7), and nucleotide-binding oligomerization

Table 1. Studies involving genetic/genomic alteration in patients with HS

Study	Methods	Main results
Theut Riis, P.[23]	Whole-exome sequencing and Mendelian analysis of 11 families with HS from Denmark.	- Mutation in the Notch pathway for all families. - Mutation in *PSENEN* and *APH1B* was found. - A causative mutation for each family was not found.
Vural, S.[13]	Sanger sequencing of all exons and exon-intron boundaries of GSC genes in 38 patients with clinically diagnosed HS.	- GSC gene mutations were detected in 3.2% of individuals with HS - Logarithm of odds never exceed 1.5: multi-genic inheritance pattern within the affected family.
Giatrakos, S.[18]	Sanger sequencing of *IL12RB1*: 139 patients and 114 healthy controls.	- No significant differences between genotype and allele frequencies between the two groups. - H1 haplotype (major frequency alleles in the studied SNPs) was associated with late-onset disease. - H2 haplotype (minor frequency alleles in the studied SNPs) was associated with a greater risk of the acquisition of Hurley III disease stage and with the involvement of a greater number of skin areas.
Giamarellos-Bourboulis, E.J.[19]	Copy number variations of *DEFB* 163 patients with HS and 185 healthy control subjects from Greece; 98 patients with HS and 329 healthy control subjects from Germany.	- Copy number was high in patients compared with controls: more than six copies were associated with a 7.53 odds ratio for HS in the Greek cohort and 5.76 odds ratio for HS in the German cohort. - Fewer than six copies of the gene were associated with earlier onset disease, less frequent presentation of skin lesions with permanent purulent discharge, and fewer affected skin areas.
Dany, M.[20]	Gene expression of enzymes involved in sphingolipid metabolic pathway in inflammatory skin lesions from 17 HS patients and 13 clinically healthy skin subjects.	HS patients had decreased expression of enzymes generating ceramide and sphingomyelin, and increased expression of enzymes catabolizing ceramide to sphingosine and of those converting ceramide to galactosylceramide and gangliosides.
Hessam, S.[21]	Expression of DNA hydroxymethylation regulators: TET and IDH family in 20 patients with HS (lesional and perilesional tissue) and 12 healthy subjects.	All genes were under-expressed in lesional HS skin. Some of them were also under-expressed in perilesional skin.
He, Y.[24]	Relation between *NCSTN* mutations and miRNA microarray expression in five familial HS patients.	*NCSTN* mutations lead to decreased miR-30a-3p levels impacting the RAB31/EGFR signaling pathway.
Rumberger, B.E.[25]	Expression of 114 genes in the skin of 34 patients with mild to severe HS and 16 healthy subjects.	129 genes were upregulated in HS skin and associated with immune activation. It includes pro-inflammatory cytokines, IL-17-associated cytokines, IL-10 family of cytokines, and IFN family members.
Zouboulis, C.C.[26]	Whole transcriptome profile of apocrine glands isolated from skin biopsies of involved and uninvolved skin of 16 HS patients.	*SULF1* is upregulated in the apocrine glands of all patients. The expression of other genes seemed to be gender-dependent.
Hessam, S.[27]	NCSTN, Notch1-3, PIK3R, and AKT mRNA and protein expression in healthy controls and lesional/perilesional skin of patients with HS.	All the studied genes are overexpressed in HS lesions. Gene expression in perilesional skin is associated with disease severity.
Ocejo-Vinyals, J.G.[22]	HLA allele distribution in 106 HS patients and 262 healthy controls from a Caucasian population.	HLA-II alleles (DRB1*07, DQA1*02, DQB1*02, and DQB1*03:01) and the DRB1*07~DQA1*02~DQB1*02 haplotype could influence resistance or susceptibility to HS

TET: ten-eleven translocation; IDH: isocitrate dehydrogenase; IFN: interferon; IL: interleukin; SULF1: sulfatase 1; HLA: human leukocyte antigen system; SNPs: single nucleotide polymorphisms.

domain-containing (NOD2)[31] in lesional and non-lesional skin[32]. Cathelicidin immunoreactivity was significantly increased both in HS epidermis and dermis, along with TNFα. This raises the question of whether the secretion of AMP by the skin could amplify cytokine production (and therefore inflammation), thus facilitating/promoting HS development[33]. Furthermore, the elevated levels of cathelicidin in HS lesions were correlated with the presence of a Th1/Th17 immune response[39].

On the contrary, decreased expression of innate defense AMP was shown in hair follicles, namely the deficient production of RNase 7 and reduced

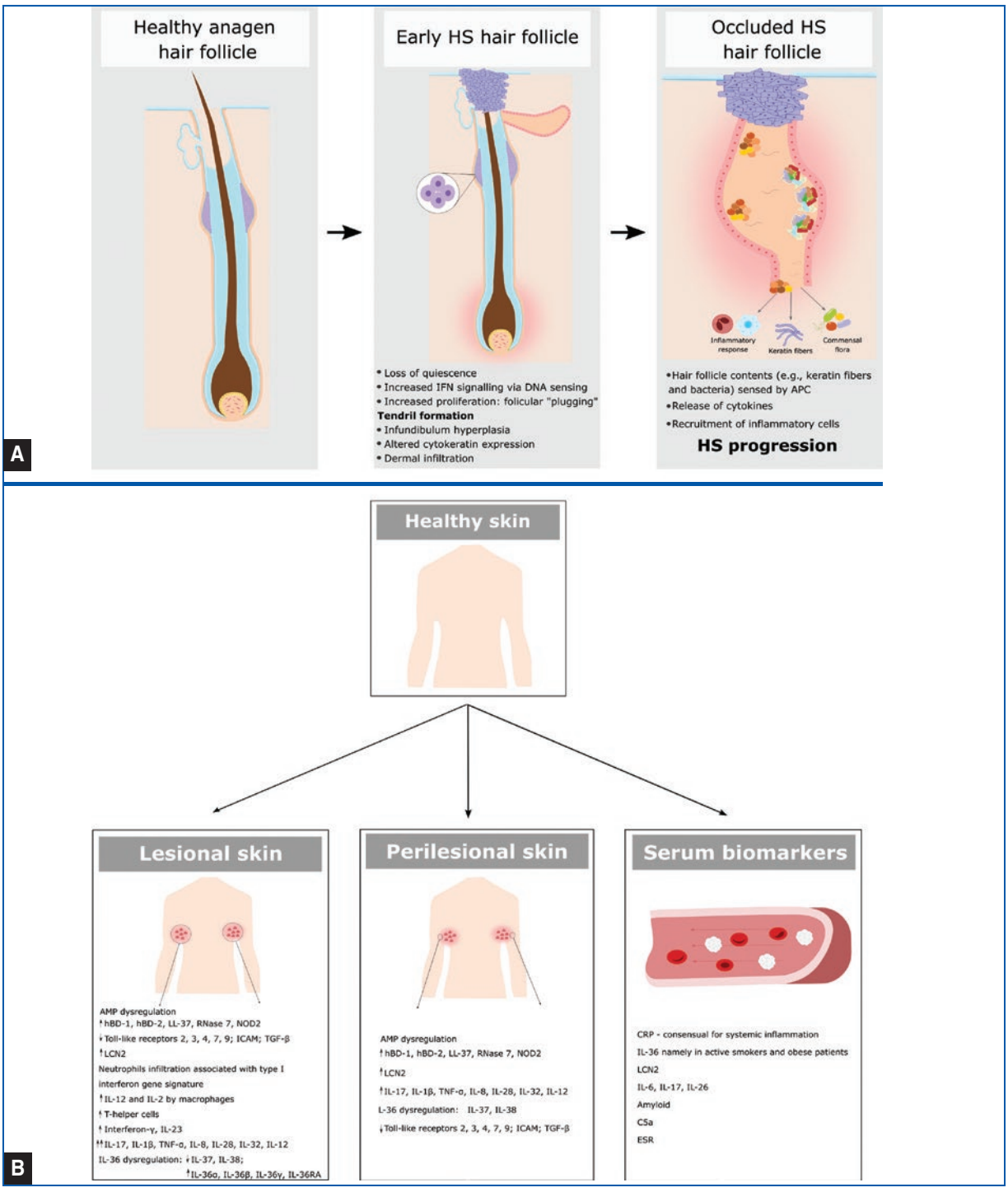

Figure 3. Initial events of HS and the contribution of the immune system to the pathophysiology of the disease. **A:** initial events of HS: The initial pathophysiology of HS is related to alterations of the infundibular epithelium that lead to follicular "plugging" and subsequent stasis of follicular content, propagation of resident bacteria, and dilation of the hair follicle unit[3-6]. IFN: interferon; DNA: deoxyribonucleic acid; APC: antigen-presenting cells. **B:** changes in immune system components in lesional, perilesional skin, and serum in HS patients. There is a dysregulation of AMP mechanisms contributing to the development of HS. Both innate and adaptive immune systems are involved in the HS process, with upregulation of pro-inflammatory cytokines in both lesional and perilesional skin. There is some evidence concerning up-regulation of serum biomarkers. Nevertheless, only high levels of C-reactive protein are consistent among patients with HS[28-42]. AMP: antimicrobial peptides; hBD: human-β-defensin; LL-37: cathelicidin; RNAase 7; ribonuclease 7; NOD2: nucleotide-binding oligomerization domain-containing 2; ICAM: intercellular adhesion molecule; TGFβ: tumor growth factor β; IL: interleukin; CRP: C-reactive protein; LCN2: lipocalin 2; c5a: complement factor C5a; ESR: erythrocyte sedimentation rate.

hBD-3 induction, which could also contribute to inflammation and HS severity[35]. High levels of lipocalin-2 (LCN2) were detected in serum and lesional skin from HS patients as a consequence of granulocyte and keratinocyte response to TNFα[36]. TNFα overproduction is also stimulated by complement factor C5a, which is activated in HS patients and may be used as a surrogate biomarker for HS[43]. Furthermore, complement factors C3a and C5a are associated with NLRP3 inflammasome, a driver of inflammation in HS[44]. Another study evaluating the presence of innate immunity markers in lesional and non-lesional skin (such as toll-like receptors 2, 3, 4, 7, and 9, intracellular adhesion molecule 1, IL-6, IL-10, TNFα, melanocyte-stimulating hormone, TGFβ, β-defensin 2 and 4, and IGF), showed a significantly decreased expression of all markers, with the exception of IL-10. Moreover, this downregulation was more pronounced in lesional skin compared to normal skin, except for TNFα[45]. Leukocyte populations seem to be dynamic in HS: in early-stage HS lesions, plasma cells are predominant, whereas in late stages, the main players are granulocytes[46].

Different studies tried to identify a cytokine profile in lesional, perilesional, and healthy skin. The IL-23/Th17 pathway has been recurrently evaluated in HS due to its important role in promoting excessive tissue inflammation. Tissue samples from lesional HS skin, compared with healthy skin, showed that IL-12 and IL-23 were abundantly expressed by macrophages infiltrating papillary and reticular dermis. Moreover, IL-17-producing T-helper cells, which are important sources of proinflammatory cytokines, were also found more often in lesional HS dermis than in healthy controls' skin[37,38,47]. Treatment with anti-TNFα drugs induces a significant reduction of cutaneous Th17 cells and was shown to balance the immune dysregulation of HS[38]. Further studies have associated the Th1/Th17 axis with the inflammatory profile of HS skin, namely through the demonstration of clustering of IL-17, interferon (IFN)—IFN-ϒ, IL-12, IL-23, IL-32, IL-1β, and TNF in lesional skin[34]. A marked upregulation of IL-17 was found in perilesional and lesional HS skin, characterized by high expression of LCN2 and high inflammatory burden[40]. A recently published study, using RNA sequencing and immunohistochemistry analysis, showed a transcriptomic and molecular profile of perilesional HS skin comparable to lesional HS skin, specifically concerning cluster of differentiation (CD)—$CD3^+$, $CD11C^+$, and neutrophil elastase-positive cellular infiltration, together with a marked upregulation of IL-17. Furthermore, the molecular levels of LCN2 could be used to group HS into two distinct subtypes: LCN2-high HS and LCN2-low HS; the former exhibits an overall higher inflammatory burden and upregulation of targetable cytokine genes, namely IFN-ϒ, IL-6, IL-1B, TNF, and colony-stimulating factor 3[40].

The levels of pro-inflammatory cytokines IL-1β, TNFα, IL-8, IL-28, IL-32, IL-23, the anti-inflammatory cytokine IL-10, and IL-6 (with both pro-inflammatory and anti-inflammatory roles) were also raised in HS lesional and perilesional skin, showing a positive correlation with disease severity[28,30,32,48-51]. This presence of pro-inflammatory cytokines beyond HS lesions could explain the high recurrence rates after surgical excision, highlighting the importance of systemic inflammation in the progression of the disease. In wound exudate samples collected from eight HS patients, IFN-ϒ levels were also significantly elevated compared to chronic wounds, demonstrating a significant inflammation[52]. IL-36 family was also dysregulated in HS lesions and perilesional skin. Interestingly, although IL-36α, IL-36β, IL-36ϒ, and IL-36Ra were overexpressed in lesional HS skin compared with healthy controls, IL-37 and IL-38 were overexpressed in perilesional skin but downregulated in lesional skin[53].

Other members of the TNF superfamily, CD27, and OX40, are preferentially expressed by skin resident regulatory T cells. Under inflammatory conditions, CD27 and OX40 lack the capacity to suppress Th17-associated genes, increasing the production of IL-17 in the skin of patients with psoriasis and HS[54].

Mesenchymal stem cells can be isolated from different tissues, including skin. There is some evidence of their involvement in the early phase of HS development. Mesenchymal stem cells isolated from the skin of 11 patients with HS exhibited elevated levels of T-cell cytokines, namely, IL-6, IL-10, IL-12, IL 17A, TNFα, TGFβ, and IFN-ϒ, showing an immune dysregulation[55]. Hair follicle stem cells and, more precisely, the outer root sheath cells isolated from HS patients had increased proliferation of progenitor cells, losing quiescent stem cells and leading to the production of type I IFNs and skin inflammation[56].

Besides inflammatory markers in lesional and perilesional HS skin, serum inflammatory markers such as IL-6, IL-17, IL-26, IL-36, C-reactive protein (CRP), serum amyloid, C5a, and erythrocyte sedimentation rate are increased in HS patients. These were pointed out as possible biomarkers of HS severity and systemic inflammatory burden[41,44,57-61]. However, this is not consensual: one recent study did not find significant differences in TNFα, IL-1β, IL-17A, or IL-23 in the serum of

HS patients; only high-sensitivity CRP (hs-CRP) can be used as an indicator of systemic inflammation[42,62].

Interleukin-36 levels were significantly higher in patients with HS who actively smoked or presented with obesity or metabolic syndrome[61].

Contrary to other cytokines, the levels of IL-22 are decreased in patients with HS and do not correlate with inflammatory status or disease severity[63]. The role of the IL-22 pathway in HS was assessed in vitro using HS keratinocytes that exhibited significantly lower levels of IL-22 compared with normal keratinocytes[64].

A comprehensive understanding of B-cells in the pathogenesis of many skin diseases, including HS, is scarce[65,66]. Some evidence shows the production of antibodies by B-cells in HS, such as IgG, IgM, anti-*Saccharomyces cerevisiae* antibodies, and aspartoacylase antibody, that could be novel biomarkers for disease severity[67]. There are also some clues demonstrating that B-cells can indirectly increase cytokine production, namely IL-10 and IL-35, and complement activation, with Bruton´s tyrosine kinase and spleen tyrosine kinase pathway activation that work as a central signal transduction network in HS, amplifying the pre-existing inflammatory response interacting with T-cells[65,67]. Despite all this data, the actual role of B-cells in HS remains unclear[65,67].

Microbiome

Evidence that implicates the involvement of the cutaneous microbiome in HS pathogenesis is recent, albeit the association between HS and bacteria has been suggested in the first reports on the disease. Microbial colonization of HS lesions has been investigated in different studies, and most patients were found to be positive for bacterial colonization[4,68,69]. Several studies reported an array of bacterial specimens sporadically isolated from lesional HS skin or exudate using traditional cultural methods. Research based on the most recent next-generation genome sequencing supports that HS patients have a distinctive skin microbiome. The evidence from traditional cultural methods and next-generation sequencing are summarized in Table 2. Bacterial colonization is significantly different in HS inflammatory lesions, HS tunnels, nonlesional HS skin, and people without HS[70].

The microbiome of HS lesions comprises predominantly aerobic bacteria such as *Corynebacterium* and anaerobes such as *Porphyromonas* spp. and *Peptoniphilus*[78]. *Acinetobacter* and *Moraxella*[71] are the main bacterial specimens found on nonlesional skin of HS patients, while *Propionibacterium* spp. and *Staphylococcus* epidermidis are skin commensals prevailing in healthy adults[71]. The anaerobic bacteria *Porphyromonas* spp. and *Prevotella* spp. were associated with HS tunnels[69].

Data concerning the presence of *Staphylococcus aureus* on HS skin are contradictory since some studies report it and others do not[4,68]. On the other hand, the carriage status of S. aureus on nasal and oropharyngeal mucosa was observed in 25% of HS patients with a prevalence of 35.3% of methicillin-resistant S. aureus (MRSA) associated with Hurley stage III[72].

Additionally, bacterial biofilms seem to have a key role in promoting inflammation and breaking the innate skin barrier[73-75]. Bacterial biofilms are found in 67%-75% of sinus tracts and infundibula and are larger in HS lesions than in perilesional skin[75]. However, in a case-control study, fewer bacteria aggregates and biofilms were detected in clinically unaffected axillary HS skin compared to healthy skin[76]. Besides these results, the bacterial composition of HS patients´ peripheral blood did not differ from healthy controls[77].

Finally, the skin-gut axis microbiome alpha diversity seemed to be lower in patients with HS. The authors speculated that this finding could be related either to disease pathophysiology or antibiotic usage[78].

Endocrinology

The association between HS and metabolic syndrome has been suggested in several studies[79-83]. Metabolic syndrome includes diabetes mellitus, hypertension, dyslipidemia, and obesity and is linked to chronic inflammation. Studies correlating obesity and HS will be further explored in the risk factors section chapter.

Thyroid hormones play a central role in metabolism, exerting pleiotropic effects on the metabolism of glucose and lipids and, consequently, on adipogenesis[84]. Therefore, their role in HS has also been addressed. Nevertheless, although thyroid disease seems to be associated with HS severity, data is not consensual concerning the impact of decreased or increased thyroid function on HS (Table 3)[84-86].

Like metabolic syndrome and thyroid function, polycystic ovarian syndrome (PCOS) has also been linked to HS, although the evidence is limited[87]. PCOS has a high comorbidity burden, and there is some overlap with HS endocrine comorbidities, such as obesity, diabetes mellitus, and metabolic syndrome[87]. Table 3 summarizes the different studies associating endocrine conditions with HS.

Table 2. Studies on the skin microbiome in HS patients

Study	Methods	Main results
Jahns, A.C.[4]	Retrospective study including archival skin appendage samples of 27 HS patients. Immunofluorescence labeling with monoclonal and polyclonal antibodies against gram-positive bacteria: Propionibacterium acnes and Propionibacterium granulosum. Fluorescence in situ hybridization for *Staphylococcus* spp. identification.	– 56% of HS patients had bacterial colonization in hair follicles and/or sinus/tract. – Most identified bacteria: coccoids (71% of the patients) in the form of biofilms and microcolonies. – *S. aureus* and coagulase-negative staphylococci were not detected in any sample.
Katoulis, A.C.[68]	Percutaneous needle aspiration of 22 HS lesions (22 patients). The collected material was cultured in aerobic and anaerobic conditions, and sensitivity tests were performed.	– 68% of the patients were culture positive. – Aerobic bacteria were present in 86% of the samples: *Proteus mirabilis*, *S. haemolyticus*, and *S. lugdunensis*. – Anaerobic bacteria were isolated in 7% of the samples: *Dermacoccus nishinomiyaensis* and *Propionibacterium granulosum*.
Guet-Revillet, H.[70]	65 adult HS patients: cultured 149 lesional skinfold samples and 175 unaffected skinfold control samples. Microbiome of 80 anaerobic lesions was compared to 88 control samples Next-generation sequencing 16S ribosomal RNA gene.	– Anaerobic bacterial cultures were detected in 83% of lesions versus 53% in controls. – Streptococci and actinomycetes were also detected in 33% lesional samples versus 26% in controls. – Next-generation sequencing identified 43 taxa associated with HS lesions: – *Prevotella* spp. and *Porphyromonas* were predominant (rare on healthy skinfolds) contrasting with a reduced population of aerobic commensals – *Prevotella* spp. and *Porphyromonas* were associated with lesional skin independently of gender, duration, and familial history of HS; – Fusobacterium and Parvimonas correlated with clinical severity of HS.
Ring, H.C.[71]	A case-control study (30 HS patients and 24 healthy controls): punch biopsy specimens from patients with HS (lesional and nonlesional) and healthy controls. Next-generation sequencing targeting 16S and 18S ribosomal RNA.	– Microbiome on lesional and nonlesional HS skin differs significantly from that in healthy controls. – Five microbiome types were identified: *Corynebacterium* species (type I); *Acinetobacter* and *Moraxella* species (type II), *S. epidermidis* (types III); *Porphyromonas* and *Peptoniphilus* species (type IV), and *Propionibacterium acnes* (type V). – In lesional skin: type I or type IV predominate. – Health controls: type IV not detected. – *Propionibacterium*: more abundant in healthy controls vs HS skin.
Ring, H.C.[76]	Case-control study (24 HS patients and 24 healthy controls) to investigate the morphology of the axillary skin microbiota by peptide nucleic acid–fluorescence in situ hybridization probes in combination with confocal laser scanning microscopy.	– In healthy controls, bacterial aggregates were found in 92% of the samples: hair follicle (64%) or at the stratum corneum (36%). The identified microorganisms were 92% cocci, 8% rods, and 35% coagulase-negative staphylococci. – In preclinical HS only three samples were positive for small cocci bacterial aggregates.
Ring, H.C.[75]	Biopsies from 42 consecutive patients with HS and chronic lesions: lesional and perilesional skin. Peptide nucleic acid-fluorescence *in situ* hybridization in combination with confocal laser scanning microscopy. Corresponding histopathological analysis on hematoxylin and eosin slides.	– Biofilms were seen in 67% of lesional samples and 75% of perilesional samples. – The mean diameter of aggregates was larger in lesional skin than in perilesional skin. – Large biofilms were mostly situated in sinus tracts (63%) or the infundibulum (37%). – Most sinus tract samples (73%) contained active bacteria that were associated with inflammation. – Abundant keratinous debris may promote biofilm formation by commensal cocci in chronic HS lesions.
Benzecry, V.[73]	A total of 46 patients with HS presented purulent or seropurulent discharge. A total of 60 samples were collected using swabs (deeply introduced in the lesions).	– 52% of the cultures were positive. – 15 bacterial species were isolated. – More prevalent species: *Proteus mirabilis* and *S. aureus*. – Positive cultures correlated with disease severity.

(continues)

Table 2. Studies on the skin microbiome in HS patients *(continued)*

Study	Methods	Main results
Ring, H.C.[77]	Case-control study: identification of bacteria in the blood of 27 moderate to severe HS patients and 26 healthy controls. Next-generation 16S ribosomal RNA gene sequencing and routine aerobic and anaerobic blood culture.	– The identification of bacterial specimens in moderate to severe HS patients' blood did not differ from healthy controls.
Ardon, C.B.[74]	Skin biopsies from active HS (inflammatory nodules and/or sinuses) and noninvolved skin from 26 patients. Specimens were cultured under optimal microbiological conditions for 24h.	– 62% of the HS patients were colonized by *S. epidermis*. – 27 different isolates from S. epidermis were identified: 59% in noninvolved skin and 41% in HS lesions. – All bacterial strains showed planktonic growth and 89% of the isolates were strong biofilm producers, *in vitro*.
Ring, H.C.[69]	Exploratory study in 32 HS patients with tunnels (17 in the groin and 15 in the axilla). Next-generation 16S ribosomal RNA gene sequencing.	– Five microbiome types were identified: *Porphyromonas* spp. (type I), *Corynebacterium* spp., (type II), *Staphylococcus* spp., (type III), *Prevotella* spp., (type IV), and *Acinetobacter* spp. (type V). – Type I and type IV (anaerobic bacteria) were the most frequent genera found in tunnels.
Katoulis, A.[72]	Observational cohort study with 68 consecutive HS patients that had not received any antibiotic therapy during the previous 3 months. Nasal and oropharyngeal sampling.	– *S. aureus* carriage was detected in 25% of the patients. – 35.3% of those had MRSA strains.
McCarty, S.[78]	Case-control study: 59 patients with HS (fecal samples, nasal, and skin swabs of affected sites) and 50 healthy controls (20 nasal and skin swabs; 30 fecal samples). Bacterial 16S rRNA gene amplicon sequencing on total DNA.	– Microbiome alpha diversity was significantly lower in the fecal, skin, and nasal samples of HS patients. – *Ruminococcus gnavus* was more abundant in the fecal microbiome of HS patients. – *Finegoldia magna* was overabundant in HS skin samples relative to healthy controls.

Risk factors

Smoking and obesity are the main risk factors identified for HS[2,85,86,94-101]. A Portuguese retrospective observational study including hospitalized patients who have been diagnosed with HS in the past five or more years showed that the most common risk factor was tobacco smoking, observed in 13.6% of the included patients[2]. In a demographically heterogeneous population-based retrospective analysis in the United States, including 7860 patients with HS, the incidence of HS among tobacco smokers is approximate twice the observed among nonsmokers[95].

A study based on questionnaires reporting the data of 129 patients diagnosed with HS, with a median follow-up of 22 years, showed that 92.2% of the patients were smokers and that among nonsmokers, 40% reported disease remission compared with 29% of active smokers. Concerning obesity, remission was reported in 45% of nonobese patients compared with 23% of obese patients[94]. Nevertheless, the role of tobacco use and body mass index (BMI) seemed to be less frequently associated with early-onset disease (≤ 17 years old)[102].

Data on early-onset disease are very limited. In a study on 134 patients, disease onset during adolescence occurred in 51.5% and was associated with female sex, family history of HS, presence of pilonidal sinus, acne conglobata, longer disease duration, and worse perception of disease severity[103]. These are important factors for the identification of individuals at high risk of early-onset and more severe disease.

The factors that determine the involvement of different skin areas in HS are not well understood. A French study based on a multivariate regression analysis of data collected from 1138 patients concluded that patients' characteristics (sex, age, BMI, family history, and smoking status), disease features (severity and other sites affected by HS), and comorbidities (arthritis, inflammatory bowel disease, acne vulgaris, acne conglobata, pilonidal disease, and dissecting folliculitis of the scalp) correlated with affected sites[104]. Two other studies, carried out in Argentina and Turkey, concluded that perianal and gluteal lesions were associated with higher HS severity, as well as male gender[96,97].

Different comorbidities have been linked to HS and could complicate the course of the disease[85,86,96,97,105-111]. Comprehensive analysis showed that the main comorbi-

dities associated with HS were acne, polycystic ovary syndrome, pilonidal sinus, metabolic syndrome, autoimmune disease, and mental health disorders[110].

Pilonidal sinus is a fistulating chronic inflammation affecting the sacrococcygeal region, which shares common histological, immunohistochemical, and ultrasound features with HS[105,109]. Moreover, solitary intergluteal HS lesions are similar to pilonidal sinus, and there is a lack of evidence confirming if they represent a spectrum of the same disease or two different entities[109]. A multicentric, cross-sectional study reported intergluteal fold lesions in approximately one-fourth of the patients with HS. Of these patients, pilonidal sinus disease was confirmed afterward in 78% of the cases. In patients in whom HS was confirmed, the lesions were associated with the proximity of the intergluteal fold, including the buttocks, genitals, and anus. Furthermore, this clinical phenotype occurs predominantly in men, at younger age, smokers, with a family history of pilonidal disease, and is associated with higher recurrence rates and severity[109]. HS, pilonidal sinus, acne conglobata, and dissecting cellulitis are diseases of the follicular occlusion tetrad[112].

Although literature reporting the relationship between acne conglobata and HS is limited[103,104], it has been associated with a higher risk of early disease onset[103] and correlated with the involvement of the sub-gluteal localization of HS[104].

Another condition that shares many aspects, namely clinical, dermatoscopic, pathogenetic, and histologic aspects with HS, is dissecting cellulitis of the scalp (DCS)[112]. HS, sinus, acne conglobata, and DCS are diseases of the follicular occlusion tetrad[112]. The prevalence of DCS among patients diagnosed with HS varies between 1-8%[97,103]. In both diseases occurs scalp perifolliculitis, and therefore some authors defend that DCS and HS should be considered the same disease affecting different localizations: scalp and apocrine gland-rich areas of the skin, respectively[97,103,112]. The likelihood of developing HS was also assessed in patients with acne vulgaris, with the association being stronger for men over 65-year-old[113]. In an Israeli population, a cross-sectional study also showed an association between acne keloidalis nuchae and HS. However, further observational studies are needed to confirm this relationship[114].

The coexistence of HS and atopic dermatitis was also demonstrated in a population-based retrospective study that included 6779 patients with HS[115]. Patients with HS were twice likely to develop atopic dermatitis compared with a control population[115]. Patients diagnosed with both diseases were predominantly female, nonsmokers, and nonobese[115]. Recently, an association between psoriasis and HS has also been addressed and demonstrated in two large-scale studies[116,117]. A study with 68,836 patients with psoriasis and the same number of healthy controls showed that the prevalence of HS is increased in patients with psoriasis. Furthermore, the coexistence of the two conditions occurred predominantly in younger patients with a higher prevalence of obesity and smoking.[117] The co-occurrence of psoriasis and HS was explored in a Danish study: HS patients had an OR of 2.99 (95% confidence interval (CI) 2.04-4.38) for having psoriasis, compared with healthy controls; on the other hand, psoriasis patients had an OR of 2.56 (95% CI 1.74-3.77) of having HS. This study showed a strong association between the two conditions[116].

The predisposition to develop HS was evaluated in patients with inflammatory bowel disease (IBD), showing that both diseases can coexist in the same patient[106,107,111,118]. A population-based study demonstrated that patients with IBD, including Crohn´s disease (CD), and ulcerative colitis, have a 9 fold higher risk of developing HS compared to the general population, particularly in females[107]. On the other hand, the predisposition to develop CD in patients with HS was also addressed in a population-based analysis in the United States[108]: patients with HS are at high risk of developing CD, approximately 3 times more likely. This association was stronger for men aged between 45 and 64 years, nonsmokers, and with perianal disease[108,111].

Stress mechanics, namely friction and skin trauma, were associated with HS based on the Koebner phenomenon. This seems to be especially relevant in obese patients[119].

Some exploratory studies tried to find biomarkers that could be considered risk factors for the development and severity of HS[120,121]: HS patients had significantly higher retinol-binding protein 4 and lower ghrelin levels, associated with an increased risk of HS[120]; an atherogenic index of plasma ≥ 0.11 was significantly and independently associated with the severity of HS[121].

Discussion

The precise pathophysiology of HS is not fully understood. In this systematic review, five main contributors to HS pathophysiology were addressed: genetics, immunity, microbiome, and endocrinology, together with the identification of risk factors/comorbidities. Mutations in genes encoding gamma-secretase, an intramembrane protease complex, are among the most commonly

Table 3. Studies reporting endocrine-related conditions in HS patients

Study	Methods	Main Results
Metabolic Syndrome		
Sabat, R.[79]	A hospital-based case-control study in 80 HS patients and 100 age- and sex-matched control patients.	– HS patients have a high prevalence of metabolic syndrome. – Role of metabolic alterations in the development of HS: central obesity (OR for HS development: 5.88); hypertriglyceridemia (OR for HS development: 2.24); HDL-cholesterolemia (OR for HS development 4.64); hyperglycemia (OR for HS development 4.09).
Gold, D.A.[80]	Retrospective chart review of 366 patient files.	– The prevalence of metabolic syndrome was 50.6% in HS patients and 30.2% in the control group ($p < 0.001$).
Miller, I.M.[81]	Cross-sectional population- and hospital-based study of HS and metabolic syndrome.	– HS appears to be associated with metabolic syndrome – Causality remains to be explored.
Shalom, G[82]	Cross-sectional study in 3297 patients with HS and 6412 age- and sex-matched control patients without HS.	– Association between HS and diabetes, hyperlipidemia, obesity, hypertension, and metabolic syndrome in HS.
Miller, I.M.[88]	Cross-sectional study in both hospital-based and population-based HS and control groups using Bioelectrical Impedance analysis to assess body composition.	– Age and sex-adjusted analysis showed a higher predicted estimated basal metabolic rate in HS patients that reflects a dysfunctional metabolism.
Vossen, A.[83]	Hospital-based cross-sectional study to classify body types (waist circumference and waist-to-hip ratio in 106 HS patients and 212 healthy controls.	– Waist-to-hip ratio did not differ in the HS group compared with the control. – A peripheral pattern of body weight distribution was seen more frequently in the HS group.
Akdogan, N.[89]	Case-control study with 40 HS patients and age- and gender-matched controls to study obesity, adipokine imbalance, dyslipidemia, pro-inflammation, and metabolic syndrome.	– HS patients have higher serum visfatin, insulin and hs-CRP levels, independent of BMI and smoking status, which are risk factors.
Jorgensen, A.R.[90]	Cohort study included 34,7200 school children that could receive a diagnosis of HS in the follow-up.	– Childhood BMI was positively and significantly associated with the risk of HS development in adulthoods.
Reichert, B.[91]	Retrospective chart view of 535 pediatric HS patients.	– 54.2% were obese and 11.6% were overweight.
Barrea, L.[92]	35 treatment-naïve HS patients and 35 controls matched for sex, age, and BMI.	– Circulating trimethylamine N-oxide positively correlated with HS Sartorius score, being a predictor of HS clinical severity.
Wright, S.[93]	Retrospective case-control analysis of 1284 patients with HS and controls matched for age, sex, and race.	– The influence of BMI may play a larger role among female and younger patients.
Polycystic ovary syndrome		
Garg, A.[87]	Cross-sectional analysis involving 22,990 patients with HS in the United States.	– Prevalence of PCOS is 9.0% among patients with HS and 2.9% in patients without the disease. – The likelihood of having PCOS in HS patients was 214 times higher than in patients without HS. – The strength of the association between HS and PCOS was similar to that of diabetes mellitus and obesity with PCOS. – A causal link could not be established.
Thyroid disease		
Miller, I.M.[84]	Retrospective comparative cross-sectional study, a population-based study compared with a control group.	– Significantly lower levels of TSH and significantly higher levels of T3 were detected in HS patients compared with the control group – HS is associated with hyperthyroidism.
Liakou, A.I.[85]	Prospective cross-sectional study with 290 patients with HS.	– Thyroid disease was associated with a higher stage of the disease.
Sherman, S.[86]	Cross-sectional population-based study including 4191 HS patients and 20,941 controls.	– HS is independently associated with hypothyroidism. – Hyperthyroidism is associated with HS only in females, middle-aged patients, and nonsmokers.

BMI: body mass index; PCO: polycystic ovary syndrome; OR: odds ratio; TSH: thyroid-stimulating hormone; T3: triiodothyronine; hs-CRP: high-sensitivity C-reactive protein.

described mutations in HS patients[8,13]. However, while up to 30-40% of patients have a positive family history of HS, only a small subset harbor genetic variants in components of the gamma-secretase complex[15]. GSC is responsible for the cleavage of several transmembrane proteins[16], and mutations in this complex result in dysregulation of Notch signaling[14]. Attenuation of Notch signaling is responsible for keratinocyte hyperplasia in the follicular infundibulum and also for changes in cytokine production by T cells[122]. However, in more than 90% of HS patients, the genetic features contributing to disease development remain largely unknown. Furthermore, the identified GSC mutations have not been found in sporadic cases of HS, which is the most common presentation. So, it is clear that efforts should be made in order to identify genetic polymorphisms that increase susceptibility to the disease, perhaps through wide genome association studies. This could improve our comprehension of HS phenotypes and disease prognosis and, together with a better understanding of immunopathogenesis, lead to the development of tailored treatments.

Hidradenitis suppurativa is characterized by inappropriate AMP secretion, and proinflammatory cytokine dysregulation[29,30,32,35]. Increased activity of dendritic cells and T cells cause keratinocyte hyperplasia via IL-23, IL-12, and Th17 immune response[30,47]. As HS progresses, increased levels of IL-1, TNF, IL-17, caspase-1, and IL-10 appear in tissue together with the recruitment of neutrophils, mast cells, and monocytes[28]. Neutrophils attracted by the IL-1-induced chemokines contribute to inflammatory cytokines production and pus formation[37,43]. LCN2 is one of the cytokines produced by neutrophils that cause inflammatory pain, and further neutrophil tissue infiltration[36,39,40]. The development of sinus tracts and scarring is associated with metalloproteinase-2, transforming growth factor beta and intercellular adhesion molecule-1[30]. Regarding serum biomarkers, only CRP has been consistently correlated with clinical inflammation in HS patients[41,42].

There is recent evidence implicating the involvement of skin microbiota in HS pathogenesis[68,69,71,72,75-77]. In HS lesional skin and nonlesional skin, there is an imbalance of skin microbiota with a predominance of anaerobes and cocci/coccobacilli bacteria[70,76]. However, there is a lack of consensus regarding which bacteria species are the most common[4,68,70,72]. In addition to the characteristic dysbiosis in HS, biofilm formation is common in HS and contributes to the rupture of the innate skin barrier and to local and systemic inflammation[74,75]. Antibiotic treatment is commonly used in HS management. Apart from its antibacterial effect, it has an immunomodulatory action. The role of antibiotic therapy and the risk of resistance induction is not well established and highlights the importance of pondering the benefit versus potential harms of antibiotic therapy in HS.

Patients with HS may be at high risk of metabolic syndrome, and clinicians should be aware of this association and be alert to the different components of metabolic syndrome regardless of the young age of the patients[81-83,94,98]. Although PCOS is associated with HS, further studies are needed to characterize the relationship between the two conditions[87]. Existing data correlating HS with other endocrinopathies, such as thyroid disease, are particularly scarce and contradictory, and a clear association cannot yet be established[84-86].

The role of lifestyle in the development of HS is well established[123,124]. HS is associated with many comorbidities, most of which are inflammatory. Tobacco smoking and obesity are strongly associated with HS[2,85,86,94-101]. Approximately 90% of patients are current or former smokers, and smoking appears to contribute to disease onset and progression[95]. The underlying mechanisms are still not clear, but nicotine is known to promote proinflammatory cytokines, induce epidermal hyperplasia, and interfere with the microbiome[93]. Obesity might contribute to HS pathogenesis through subclinical inflammation, metabolic changes, and friction[99,100].

In conclusion, HS is a chronic, inflammatory, debilitating disorder. HS etiopathogenesis has not been entirely elucidated. This systematic review updated the most recent understanding of HS pathogenesis, integrating inflammatory pathways that include genetics, immunity, endocrinology and microbiome. Other contributing factors identified as HS risk factors and comorbidities were discussed and included in this cohesive multifactorial model. Despite the vast increase in knowledge in the last few years, there is much to unveil in the comprehension of this highly complex and multifactorial disease.

Conflicts of interest

Pedro Mendes Bastos has received honoraria for acting as a consultant and/or as a speaker for AbbVie, Janssen, Novartis, LEO Pharma, Almirall, Sanofi, Viatris, L'Oréal and Cantabria Labs. He has also worked as a principal investigator in clinical trials supported by Pfizer, AbbVie, Sanofi, and Novartis. Joana Cabete has received honoraria for acting as a consultant and/or as a speaker for Novartis and Abbvie. She has worked as investigator

in clinical trials supported by Novartis. The remaining authors have no conflicts of interest to declare.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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